

REMARKS

I. Status of the Claims

Claims 1-24 were canceled in a preliminary amendment. Claims 25-27 are currently pending under examination.

II. Claim Rejection

35 U.S.C. §103(a)

In the final Office Action mailed December 19, 2006, the Examiner maintains the rejection of claims 25-27 under 35 U.S.C. §103(a) for alleged obviousness. Specifically, the Examiner asserts that the claims are obvious over U.S. Patent No. 5,099,005 (the '005 patent) in view of Kim *et al.*, U.S. Patent No. 6,358,710 (the '710 patent), Pierce Product Information for ImmunoPure IgG1 Fab and F(ab')₂ preparation kit (Pierce Product Information), and U.S. Patent No. 4,281,061 (the '061 patent). Applicants respectfully traverse the rejection.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

The present invention relates to a kit for making F(ab')₂ fragments from a glycosylated antibody comprising a hinge region. The hinge region contains one or more protease cleavage sites and has one or more adjacent non-hinge regions, which contain one or more attached oligosaccharide groups. The oligosaccharide group(s) cause the protease cleavage site(s) within the hinge region to be resistant to a protease treatment. There are at least two components in the claimed kit: first, a deglycosylation composition comprising at least one glycosidase capable of catalyzing the hydrolysis of an N-glycosidic or O-glycosidic linkage between a sugar unit and an amino acid to form a partially or wholly deglycosylated antibody; and, second, a protease composition comprising one or more proteases capable of reacting with

said partially or wholly deglycosylated antibody to produce said F(ab')₂ fragments from said partially or wholly deglycosylated antibody.

In contrast, the cited references teach the following: the '005 patent relates to methods of enhancing immunoglobulin fragment yield, which include the step of desialylating the immunoglobulin; the Kim *et al.* reference reports the observation of O-linked glycosylation in the hinge region of mouse IgG2b, which the authors believe renders the hinge region resistant to proteolysis of the heavy chain; the '710 patent describes humanized NR-LU-13 antibodies and discusses the possible modification of the antibody's glycosylation status; the Pierce Product Information provides description of a kit for preparing IgG1 Fab or F(ab')₂, which contains proteases and instructions but no enzyme for deglycosylation; and the '061 patent does not directly relate to the elements of the pending claims and is cited, according to the Examiner, to show that "components or reagents can be provided as kits as a matter of convenience, optimization and economy of the users" (page 4, lines 1-2, of the Office Action mailed June 23, 2006).

For reasons already set forth in Applicants' submissions of May 23, 2006, and September 19, 2006, Applicants contend that, when viewed together, the cited references fail to provide all limitations of the pending claims. Applicants further contend that, even assuming all limitations could be found in the cited references, these references would nonetheless fail to provide any motivation or suggestion to combine the limitations. In particular, the '005 patent teaches away from the present invention by suggesting desialylation, not deglycosylation, as an important step in effective production of immunoglobulin fragments. It is therefore Applicants' position that no *prima facie* case of obviousness has been established.

In the final Office Action mailed December 19, 2006, the Examiner has raised some specific points in sustaining the obviousness rejection. First, the Examiner challenges Applicants' contention that the '005 patent teaches the use of sialidase only, stating that the use of pepsin or papain is also described in the '005 patent (the second paragraph on page 3 of the final Office Action). The Examiner's statement is, however, an irrelevant truth. When Applicants

pointed out that the '005 patent teaches the use of sialidase only, the argument was made in the context of enzymatic treatment for the purpose of desialylation or deglycosylation, not for the purpose of protein digestion. The use of an enzyme for desialylation (*i.e.*, a sialidase) or an enzyme for deglycosylation (*i.e.*, a glycosidase) relates to the removal of various sugar residues attached to an antibody, a step performed prior to digesting the antibody with one or more proteases that cleave the antibody into desired fragments (*e.g.*, F(ab)'2 fragments). Thus, whether or not the '005 patent teaches the use of any protease is irrelevant to Applicants' arguments regarding the question of obviousness.

Second, the Examiner asserts that, in the Kim *et al.* reference, the structural limitation of antibody having one or more non-hinge regions, which are adjacent to the hinge region and contain one or more attached oligosaccharide groups is an inherent property of the antibody (the second paragraph on page 3 of the final Office Action). Applicants respectfully disagree with the Examiner. As it is well settled in case law, although an anticipation rejection can be based on the inherency theory, an obviousness rejection requires that all claim limitations to be expressly disclosed; in other words, if a relevant limitation is inherent, or unrecognized, there can be no basis to support any motivation to combine this limitation with others.

Third, the Examiner asserts that even though the '710 patent provides only general knowledge in the field of protein glycosylation, an ordinarily skilled artisan would still be motivated to "extrapolate the deglycosylation method in the protein field to deglycosylation of antibody using glycosydases" (the three paragraph on page 3 of the final Office Action). Applicants again respectfully disagree with the Examiner. As established by the prevailing case law, the obviousness determination must be made when the claimed invention is considered as a whole, the references are considered as a whole, and the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. See, *e.g.*, *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187n5 (Fed. Cir. 1986), and MPEP §2141 II. When all evidence, particularly the explicit teaching away from deglycosylation of antibodies by the '005 patent, is considered together, the conclusion of obviousness is untenable.

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As such, Applicants contend that no showing of *prima facie* obviousness has been made. The withdrawal of the obviousness rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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